Although the Office Action of June 24, 1999 states that completed copies of forms PTO-1449 are attached, copies of those forms were not attached and **have not yet been received** by Applicant. Applicant requests that copies of completed forms PTO-1449 be furnished for Applicant's files.

Claims 1-3 are rejected under 35 U.S.C. 103(a), as being unpatentable over Kermode (1991) alone or in view of Gleisner (1981). In formulating the rejection, the examiner alleges that:

> ***[T]he knowledge that formyl peptides stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms would be sufficient motivation to an artisan to apply such agent as a pharmaceutical under conditions when **therapeutic stimulation** of such defense reaction to infectious microorganisms is required.*** [Emphasis added.]

Applicants respectfully traverse the rejection.

Neither of the cited art teach or suggest that a pharmaceutical composition comprising a pharmacological carrier and a peptide having the formula f-Met-Leu-Phe-Phe has **anti-inflammatory** activity .

Kermode teaches that fMLP peptides are **proinflammatory** due to their ability to stimulate chemotaxis and mast cell degranulation (page 721, right column, lines 41-53).

> ***__Binding of a formyl peptide agonist to the receptor causes its conversion to a high-affinity state and triggers an immediate signal for degranulation__**; this biological response thus parallels high-affinity binding. When the agonist is a less potent formyl peptide (such

> as fMet-Leu-Phe), this activated state is maintained only for a short time; a rapid transition occurs to a lower-affinity state incapable of sustaining a chemotactic signal (Fig. 6a). This transition does not affect the degranulation signal, but restricts the longer-duration signal for the chemotactic response; migration is thus limited. **The most potent analogues (such as fMet-Leu-Phe-Phe), in contrast, stabilize the activated high-affinity state in some way, thereby providing a longer duration signal and greater migration**.***(emphases added)

Furthermore, Kermode establishes that different fMLP peptides have widely differing affinities for the fMLP peptide receptor (page 718, left column, lines 5-9).

> The equilibrium dissociation constant (K_d) for high-affinity binding had a range of **1300-fold** between the least potent (fVal-Leu-Phe) and the most potent (fMet-Leu-Phe-Phe) of the seven formyl peptide analogues, whereas the K_d for the low-affinity binding varied **9700-fold** (Table 1).***[emphasis added]

Finally, Kermode states that the strength of the binding of the fMLP peptide to the receptor correlated to the biological potency (i.e. its ability **stimulate** mast cell degranulation and chemotaxis to the site of inflammation) of the peptide (abstract, page 715, lines 5-6):

> ***The relative potencies of the formyl peptide analogues for stimulation of degranulation correlated will with their relative potencies for high-affinity, but not low-affinity, [receptor] binding.***

Thus, from Kermode, we learn that fMLP peptides have a **proinflammatory** activity and that fMLPP, a peptide of the presently claimed invention, is particularly potent in this regard. Furthermore, we learn that the different fMLP peptides have a wide range of affinities for the receptor and that this in turn means their biological potencies vary widely.

The examiner asserts that "the knowledge that formyl peptides stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms would be sufficient motivation to an artisan to apply such agent as a pharmaceutical under conditions when **therapeutic stimulation** of such defense reaction to infectious microorganisms is required." However, such formyl peptides are taught to be **proinflammatory**. Although inflammation initiates a defense reaction, stimulating inflammation *per se* is not desirable. The examiner fails to provide any reference teaching that stimulating an inflammatory cascade is a desirable therapeutic goal.

The formyl peptides and their proinflammatory activity have been known for many years. However, none of the cited references teach or suggest using them for any therapeutic purpose. Indeed, until the teaching of the present application, there has been no suggestion for making a pharmaceutical composition containing any formyl peptides, much less the specific peptides recited in the present claims.

Certainly, Kermode does not teach or suggest to one of ordinary skill in the art that a pharmaceutical composition comprising a pharmacological carrier and a peptide having the formula f-Met-Leu-X, wherein X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe and Phe-Tyr would be useful for any therapeutic purpose, much less that such composition has an **anti-inflammatory** activity . In fact, Kermode teaches that such peptides have **proinflammatory** activity.

Gleisner (1981) ***fails*** to make up for the deficiencies of Kermode (1991). Gleisner suggests that f-Met-Leu-Phe can have an inhibiting effect on mast cell degranulation in an *in vitro* test, but fails to show this for other formyl peptides. It is **not** obvious that structurally similar compounds will have the same effect **or** the same potency, if any effect or potency at all. That conclusion is supported by the study of Kermode, where they observed large differences in potency of various formyl peptides. In this respect, however, it should be noted that the potency of activation of neutrophils by various peptides described in Kermode **cannot** be used to correlate the effect on the inhibition of mast cells. In fact, Gleisner admits that they have not tested other formyl peptides for inhibition potential (page 16, lines 6-8):

> In this report we have **not** considered in detail the relative potencies of f-methionyl peptides and pepstatin because the blueing reaction is only semiquantitative. [Emphasis added].

In fact, Gleisner (1981) did not test any of the peptides of the presently claimed invention. Further, the more recent cited references, which do mention a peptide of the presently claimed invention (Kermode (1991), Ferry (1989) and Anderson(1992)), teach that this peptide has **pro**-inflammatory activity, not anti-inflammatory activity as taught and claimed herein.

What reason would one of ordinary skill in the art have to make a pharmaceutical composition of the presently claims formyl peptides in view of the teachings of Gleisner and Kermode? No viable reason can be found in the teachings of Gleisnar and Kermode? In addition, the teachings of Anderson and Ferry further

reinforce the teachings of Kermode. It is respectfully submitted that one of ordinary skill in the art, taking in to account the teachings of the totality of the cited references, would consider the formyl peptides to be **pro**-inflammatory. It is further submitted that one of ordinary skill in the art would not consider using the formyl peptides for any therapeutic purpose.

Kermode teaches that the fMLP peptides have a wide variety of biological activities. Furthermore, the present disclosure teaches that the anti-inflammatory activities of the formyl peptides vary widely depending on their particular sequence (see Table 1, page 19). For example, the fMLP peptide taught by Gleisner had a 30% mast cell degranulation inhibitory activity while the closely related fMLPK or fMLYY had no inhibitory activity. However, Applicants found that several peptides, for example fMLY and fMLPP, had surprisingly superior mast cell degranulation inhibitory activities, 55% and 100% respectively.

Thus, based on the teachings of Kermode in view of Gleisner, one of ordinary skill in the art would not have been motivated to develop a pharmaceutical composition having anti-inflammatory activity. Furthermore, the surprisingly remarkable inhibitory activities of the peptides of the present invention would not have been obvious to one of ordinary skill in the art from the prior art teachings.

Applicants have tested the effects on inflammation induced by prior art peptides, namely fMLP discussed in Gleisner and other references, as compared to

peptides of the present invention, namely fMLPP. The results of these experiments are presented in the accompanying Declaration of Dr. Clagett. Briefly, Applicants compared the effects of injecting fMLP or fMLP + fMLPP into the dorsum of mice feet and observed the effects on the injected tissue over time. Applicants found that injection of fMLP alone caused a strong inflammatory effect including massive cellular infiltration to the site of injection whereas simultaneous injection with fMLPP blocked this inflammatory response.

In short, fMLP exhibited a **pro**-inflammatory activity in accord with the teachings of the prior art. However, surprisingly and unexpectedly (in view of the prior art) fMLPP exhibited an **anti**-inflammatory activity and that blocked the pro-inflammatory response induced by fMLP.

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejections are requested.

Claim 1 is rejected under 35 U.S.C. 103(a), as being unpatentable over Kermode and Ferry, *supra*, in view of Anderson.

In formulating the rejection, it is alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to be motivated to make substitutions in the peptides reported by Kermode or Ferry because Anderson teaches the requirements

for the structure of biologically active formyl methionyl peptide analogs.

Applicants respectfully traverse the rejection. Kermode is discussed in detail above. It is not seen where Ferry and Anderson make up for the deficiencies of Kermode.

Neither Ferry nor Anderson teach or suggest a pharmaceutical composition comprising a pharmaceutical carrier and a peptide having the formula f-Met-Leu-Phe-Phe, particularly such a composition having anti-inflammatory activity.

As noted above, Kermode teaches that fMLP peptides have **proinflammatory** activity and that different fMLP peptides have a wide range of biological potencies in regards to their ability to induce mast cell degranulation and chemotaxis to the site of inflammation.

The Ferry reference is directed to a study of the factors affecting intestinal adsorption and enterohepatic circulation of N-formyl peptides (page 61, Abstract, last sentence).

> ***Abnormalities of the intestinal mucosal barrier to proinflammatory bacterial peptides could play a role in inflammatory disorders of the gut.

Thus, from Ferry, we learn that fMLP peptides are **pro**inflammatory and that they are potentially involved in inflammatory disorders. Certainly, based on the

teachings of Ferry, one of ordinary skill in the art would not have been motivated to make a pharmaceutical composition for the treatment of inflammatory disorders using a peptide which has been suggested to be involved in causing inflammatory disorders.

Anderson is directed to the study of the structural requirements of N-formyl peptides for **hepatobiliary secretion** (see page 248, Abstract, lines 3-6).

> ***To determine the molecular structural requirements for hepatobiliary excretion of formyl-methionyl peptides, structure-activity studies using portal venous infusions of 24 structural analogs of formyl-met-leu-tyr were performed in rats with biliary cannulae.***

Anderson further teaches that there is no basis for correlating the ability of the liver to excrete N-formyl peptides with the bioactivity (i.e. mast cell degranulation and chemotaxis) of the N-formyl peptides themselves. At page 254, left column, 4th full paragraph:

> Our studies, while confirming the importance of N-acylation of peptides in hepatic extraction and excretion, **do not** elucidate the mechanism of uptake and transport.***[emphasis added]

And, at page 254, right column, last paragraph:

> ***[S]ince both trace [quantity] and mass [quantity] infusions of peptides were equally excreted into the bile, the efficiency of secretion **did not correlate** with bioactivity (e.g. FMLT vs nonbioactive FMLT sulfoxide) and excretion of peptide was complete within several minutes, too short a time scale for leukocyte recruitment.

Thus, Anderson teaches the "requirements for the core structure of biologically active formyl Met peptide analogs", wherein the **biological activity**, to which

reference is made, **is the ability of the peptides to be excreted by the liver**. Anderson teaches nothing about the requirements for the core structure of biologically active peptide analogs wherein the biological activity, to which reference is made, is related to inflammation (i.e. mast cell degranulation and chemotaxis). In fact, Anderson teaches that the mechanism by which N-formyl peptides are excreted by the liver is unkown and may be totally separate from the mechanism by which they are involved in the inflammatory response. Thus, even if one of ordinary skill in the art wanted to stimulate inflammation activity, when studying the biological activity of N-formyl peptides (i.e. degranulation and chemotaxis), he would not have been motivated to make the substitutions as taught by Anderson for stimulating inflammation activity because Anderson teaches that excretion of, and stimulation of inflammation by, the peptides may occur by different mechanisms.

Further, there is no suggestion, whatsoever, in the cited art regarding the structure required for anti-inflammatory activity. Thus, even if Anderson had taught the structural requirements for biological activity related to induction of inflammation (i.e. mast cell degranulation and chemotaxis), one of ordinary skill in the art modifying the peptides of Kermode or Ferry would have been expected at most to produce **proinflammatory** peptides, **not** the **anti**-inflammatory peptides of the present invention.

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the

rejections are requested.

Claims 1-3 are rejected under 35 U.S.C. 103(a), as being unpatentable over Gleisner (1981) in view of Kermode (1991), Ferry (1989), and Anderson (1992).

In formulating the rejection, it is alleged that:

> ***[T]he Gleisner reference provides motivation to one of ordinary skills in the art to formulate pharmaceutical compositions of formyl Met peptides to prevent degranulation of mast cells in the course of inflammatory disorders and thus to inhibit cytokine/histamine release which is a desirable pharmacological effect. Kermode, Ferry and Anderson teach various representatives of f-met peptides as discussed above.

Applicants respectfully traverse the rejection.

As noted above, Gleisner suggests that f-Met-Leu-Phe may have an inhibiting effect on mast cell degranulation but fails to show any inhibiting effect for other formyl peptides. Indeed, Gleisner did not test any of the peptides of the presently claimed invention and the references, which do mention peptides of the claimed invention and which are later than Gleisner, teach that these and other formyl peptides have **pro**inflammatory activity.

Kermode teaches that fMLP peptides have **proinflammatory** activity and that different fMLP peptides have a wide range of biological potencies in regards to their ability to induce mast cell degranulation and chemotaxis to the site of inflammation.

Ferry also teaches that formyl peptides have **proinflammatory** activity.

Anderson teaches that formyl peptides are **proinflammatory** but, as discussed above, does not set forth the structural requirements of formyl peptides in regard to proinflammatory activity.

In view of the prior art of record, it is apparent that one of ordinary skill in the art would have no expectation about that fMLP could be useful for the treatment of inflammation because all of the presently claimed peptides, which were previously studied, were shown to have proinflammatory activity.

Only present Applicant has discovered the usefulness of the claimed invention as a pharmaceutical composition and having **anti**-inflammatory activity. Further, as shown in Table 1, many formyl peptides have no effect on inhibition of mast cell degranulation. fMLP has an effect of only 30% inhibition of mast cell degranulation in the *in vitro* test. Surprisingly and unexpectedly, the compounds of the present invention have an effect of 55% or more inhibition of mast cell degranulation with the preferred f-Met-Leu-Phe-Phe providing 100% inhibition of mast cell degranulation in the *in vitro* test.

Furthermore, as discussed above, Applicants have tested the effects on inflammation of subcutaneous injection of fMLP as compared to fMLP + fMLPP into the dorsum of mice feet. Applicants found that fMLP (the prior art peptide) had **pro-**

inflammatory activity while fMLPP (a peptide of the present invention) had **anti**-inflammatory activity. These *in-vivo* test results are presented in the accompanying Declaration of Dr. Clagett. Thus, Applicant's invention has surprising and unexpected results, when compared to the prior art.

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejections are requested.

Claims 1 and 4-8 are rejected under 35 U.S.C. 103(a), as being unpatentable over Kermode, Ferry, Anderson, and Gleisner as applied to claims 1-3 above, and further in view of Goodman and Gilman.

Applicants respectfully traverse the rejection. Kermode, Ferry, Anderson, and Gleisner are discussed in detail above. It is not seen where Goodman and Gilman make up for the deficiencies in Kermode, Ferry, Anderson, and Gleisner.

Neither Goodman nor Gilman teach or suggest a pharmaceutical composition comprising a pharmaceutical carrier and a peptide having the formula f-Met-Leu-Phe-Phe, much less a composition having **anti-inflammatory** activity.

As noted above, given the many teachings that f-met peptides are **pro**inflammatory, one of ordinary skill in the art would not have been motivated to

make and use a pharmaceutical composition of any kind, much less one having **anti**-inflammatory activity, comprising the formyl peptides of the present invention. Thus, the lack of motivation to develop and pharmaceutical compositions containing f-Met peptides encompasses all routes of administration. It makes moot the rejection relying upon Goodman and Gilman.

In view of the above, it is not seen how the present invention would have been obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the rejections are requested.

Claims 1-8 are rejected under 35 U.S.C. §112, first paragraph, because it is alleged that the claims do not reasonably provide enablement for pharmaceutical use of f-met peptides in general.

Applicants respectfully traverse the rejection.

Applicants provide considerable discussion for making pharmaceutical compositions of the invention, including dosage. See pages 11-15. Further, an extensive experimental section presents detailed descriptions and results of *in vitro* and *in vivo* experiments showing the administration of a formyl peptide of the invention can inhibit mast cell degranulation, eosinophil infiltration and mucus accumulation. They present data from mouse models of asthma (pages 35-39). Furthermore, they provide the dosage used for treatment of the mouse model of

asthma (10 μg injected into mouse ~25 g or 400 μg/kg, at page 37, line 22) and the mouse model of arthritis (100 μg into a 25 g mouse or 4,000 μg/kg, at page 40 lines 6 and 15), which is within the effective range indicated in the specification at page 11.

The examiner admits that "selection of a route of administration and appropriate carriers is an art-recognized result-effective variable which would have been routinely determine and optimized in the pharmaceutical art" [page 8 of the Office Action]. The same can certainly be said of determining an effective dosage. Performing a dose response curve for determination of an optimal dosage would hardly require undue experimentation for one skilled in the art. Indeed, routine experimentation is normal for establishing doses for therapeutic treatments.

The examiner states that "[t]he instant specification does not provide guidance for the selection of the range of pharmaceutical effect." The examiner assumes that the disclosed range "will most likely encompass both the ranges of inoperative and harmful effects." Applicants submit that it is routine experimentation in the art to determine the useful dose for any particular application and to determine whether a dose has any harmful effects. Applicants have found anti-inflammatory effect at very low doses and surprisingly have not found any harmful effects even at high dosages in animal testing to date.

It is respectfully submitted that the description and working examples in the specification provide adequate guidance for one skilled in the art to make and use the

claimed invention. In light thereof, reconsideration and withdrawal of the §112 rejections are respectfully requested. If the examiner intends to maintain this rejection, it is requested that specific reasons be set forth regarding why the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims so that applicant can specifically address each such reason.

In view of the amendment and discussion above, and the Declaration of Dr. Clagett, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Respectfully submitted,

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